



Interneuron Progenitor Transplantation to Treat CNS Dysfunction

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Due to the inadequacy of endogenous repair mechanisms diseases of the nervous system remain a major challenge to scientists and clinicians. Stem cell based therapy is an exciting and viable strategy that has been shown to ameliorate or even reverse symptoms of CNS dysfunction in preclinical animal models. Of particular importance has been the use of GABAergic interneuron progenitors as a therapeutic strategy. Born in the neurogenic niches of the ventral telencephalon, interneuron progenitors retain their unique capacity to disperse, integrate and induce plasticity in adult host circuitries following transplantation. Here we discuss the potential of interneuron based transplantation strategies as it relates to CNS disease therapeutics. We also discuss mechanisms underlying their therapeutic efficacy and some of the challenges that face the field.

Keywords: stem cell therapy, GABA, medial ganglionic eminence, excitation-inhibition, neuropsychiatric disorders

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INTRODUCTION

Since the turn of 20th century neural transplantation has been studied as a potential therapeutic strategy for neural reconstruction and repair (Cajal, 1928). Initial attempts with engraftment of neural tissue in lower vertebrates remained largely unsuccessful with most studies concluding that the adult brain was inhospitable for graft survival (Willis, 1935). However, several early studies showed promise with engraftment of developing tissue (Dunn, 1917; Tidd, 1932; Clark, 1940). Notably, one study (Clark, 1940) demonstrated viability of embryonic neocortical grafts dissected from 15 to 20 days old embryos transplanted in the young mammalian brain. Strikingly, the engrafted cells differentiated and migrated such that the graft showed laminar features and cell morphologies characteristic of the developing cerebral cortex. Later, transplanted neonatal and embryonic cells were shown to develop normal synaptic afferent and efferent connections with host brain and spinal neurons (Björklund et al., 1976; Lund and Hauschka, 1976; Jakeman and Reier, 1991). Moreover, differentiation and integration of transplanted cells within the adult striatum and hippocampus was shown to be associated with improvements in motor coordination and spatial learning (Low et al., 1982; Gage et al., 1983, 1984; Björklund and Stenevi, 1984). Later studies revealed details of the anatomical and functional integration of the grafted tissue into host circuits: neurons within intraspinal grafts that were effective in improving motor function were shown to extend axons along white matter tracts rostrally and caudally (Nornes et al., 1983; Jakeman and Reier, 1991; Li and Raisman, 1993), and form synaptic relays (Cummings et al., 2005; Lu et al., 2012). Together, these studies revealed wide ranging potential for neural stem cell transplantation in CNS disease therapeutics.

FACTORS AFFECTING VIABILITY AND FUNCTIONALITY OF A NEURONAL TRANSPLANT

In several studies the ideal age of embryonic donor tissue has been shown to depend on the developmental stage of the donor tissue, the time window including neuronal proliferation and migration being optimal (Banker and Cowan, 1977; Kromer et al., 1983). This is consistent with the finding that isolated hippocampal neurons that have recently completed DNA synthesis and are in the process of migration showed long term survival in cultures as opposed to post-mitotic cells dissociated from the ventricular zone or the cortical plate (Banker and Cowan, 1977). Other favorable attributes of young tissue may include their relative insusceptibility to transplant procedure related trauma, as well as their particularly low O₂ consumption rate which may buoy their viability in new environments during the initial days after implantation (Shyh-Chang et al., 2013).

A major objective of transplant studies has been to determine factors that allow the grafted cells to integrate functionally into host circuits, as such integration is thought to be important for sustainable therapeutic effects. In early studies it was noted that some types of transplanted embryonic cells displayed minimal dispersion, with functional effects often limited to graft site. For example, while cells within embryonic nigral tissue grafted into the striatum of 6-OHDA lesioned rats differentiate into dopamine neurons, the neurons do not disperse, but rather form a dopamine “island” near the site of transplantation within the striatum. Considering these observations, major factors contributing to a transplant’s long term functionality would be the age of donor tissue, its ability to demonstrate widespread dispersion and integration within host, as well as the use of disease relevant cell types.

INTERNEURON PROGENITORS AS A CANDIDATE FOR CELL BASED THERAPY

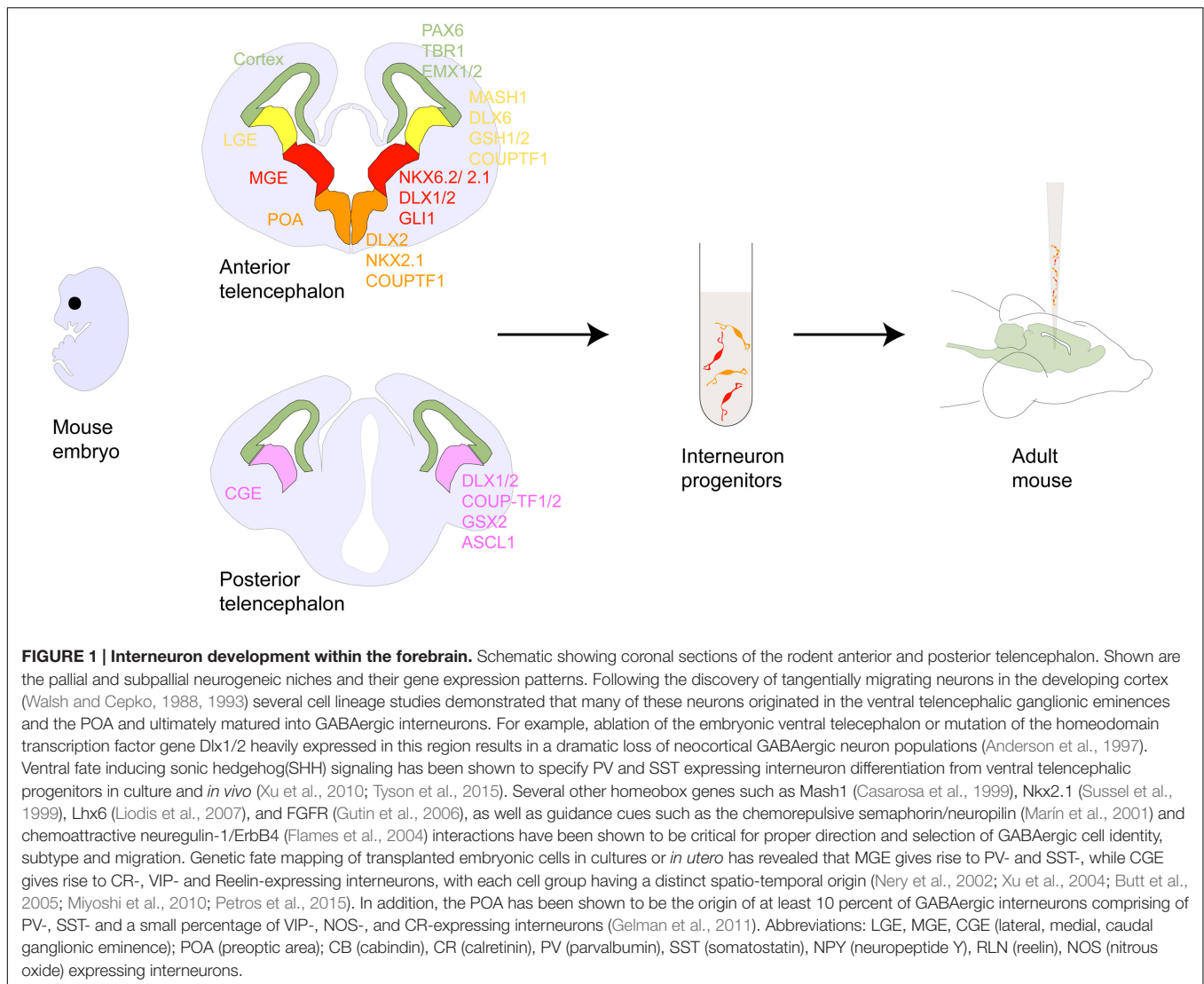
While the early studies served as proof-of-principle for the concept of cell based therapy, mechanisms by which transplanted cells modify diseased brain circuitries have remained largely unknown. With refined knowledge of neurodevelopment (Merkle and Alvarez-Buylla, 2006; Muotri and Gage, 2006; Fuentealba et al., 2015) studies carried out over the past two decades have now begun to offer mechanistic insights and renewed evidence for the therapeutic efficacy of cell transplantation in CNS diseases. Of particular relevance has been the use of γ -amino butyric acid (GABA)-ergic inhibitory neuron precursors (Wonders and Anderson, 2006; Tricoire et al., 2011; Southwell et al., 2014) (Figure 1). Constituting only about 20% of the adult cortical neuronal population, inhibitory neurons are potent regulators of normal brain function, sculpting the excitation-inhibition balance and entraining activity of neuron ensembles in brain circuits (Klausberger et al., 2003; Klausberger and Somogyi, 2008; Lewis et al., 2012). Maturation of GABA circuits has

been shown to set off and regulate critical period plasticity in brain sensory systems, offering a putative neurobiological handle with which to interrogate neurodevelopmental origins of neurological disorders (Hensch, 2005). As such imbalances in excitation-inhibition and dysfunction of inhibitory interneurons are hypothesized to underlie several neurological disorders like schizophrenia (SCZ; Harrison, 2015), autism spectrum disorders (Peñagarikano et al., 2011), Alzheimer’s disease (AD; Andrews-Zwilling et al., 2010), Parkinson’s disease (PD; Salin et al., 2009), epilepsy (Möhler et al., 2004), and neuropathic pain (NP) (Moore et al., 2002).

EPILEPSY

Impaired inhibition has been described as a key pathognomonic feature in animal models of (Sloviter, 1987; Cossart et al., 2001) and human patients with (de Lanerolle et al., 1989; Mathern et al., 1995) epilepsy. For example, studies in temporal lobe epilepsy, the most common type in adults, have revealed deficits in hippocampal pyramidal neuron distal dendritic domain-targeting interneurons, including interneuron subpopulations expressing somatostatin (SST; Buckmaster and Jongen-Rêlo, 1999; Cossart et al., 2001; Kobayashi and Buckmaster, 2003), neuropeptide Y (NPY; Mathern et al., 1995; Sundstrom et al., 2001), and calbindin (CB; Wittner et al., 2002). In addition, a decrease in the density of hippocampal basket and chandelier parvalbumin (PV) immunoreactive cells has been reported (DeFelipe, 1999; Arellano et al., 2004; Ogiwara et al., 2007); however, perisomatic GABA innervation appears to be intact (Wittner et al., 2001, 2005). Despite compensatory sprouting of interneurons (Mathern et al., 1995; Arellano et al., 2004) imbalances in input-output relationship of pyramidal cells (Cossart et al., 2001) result in abnormal cortical network activity (Ogiwara et al., 2007). Introducing functional GABAergic neurons hence provides a means of replacing lost or dysfunctional inhibitory cells and tempering increased electrical activity seen in epilepsy.

Many of the early interneuron progenitor transplantation studies were carried out in animal models of epilepsy. Alvarez-Dolado et al. (2006) provided the first electrophysiological evidence of functional integration of MGE derived neuronal precursors grafted into the juvenile brain. In this study, grafted MGE cells within the hippocampus migrated up to ~5 mm from injection site at 2 months after transplantation, acquired molecular markers of mature GABAergic interneurons [by expressing GABA, PV, SST, calretinin (CR), and NPY] and increased GABA mediated synaptic inhibition in regions containing transplants. In a series of follow-up studies, therapeutic efficacy of MGE progenitors was demonstrated by the reduction of severity and frequency of seizures in genetic (Baraban et al., 2009; Hammad et al., 2015) and acquired (Hunt et al., 2013; Henderson et al., 2014; Jaiswal et al., 2015) rodent models of epilepsy and hippocampal disinhibition (Calcagnotto et al., 2010; Waldau et al., 2010). Notably, while MGE cell transplantation in the hippocampus increased inhibitory post-synaptic current (IPSC) frequencies in host pyramidal (Baraban

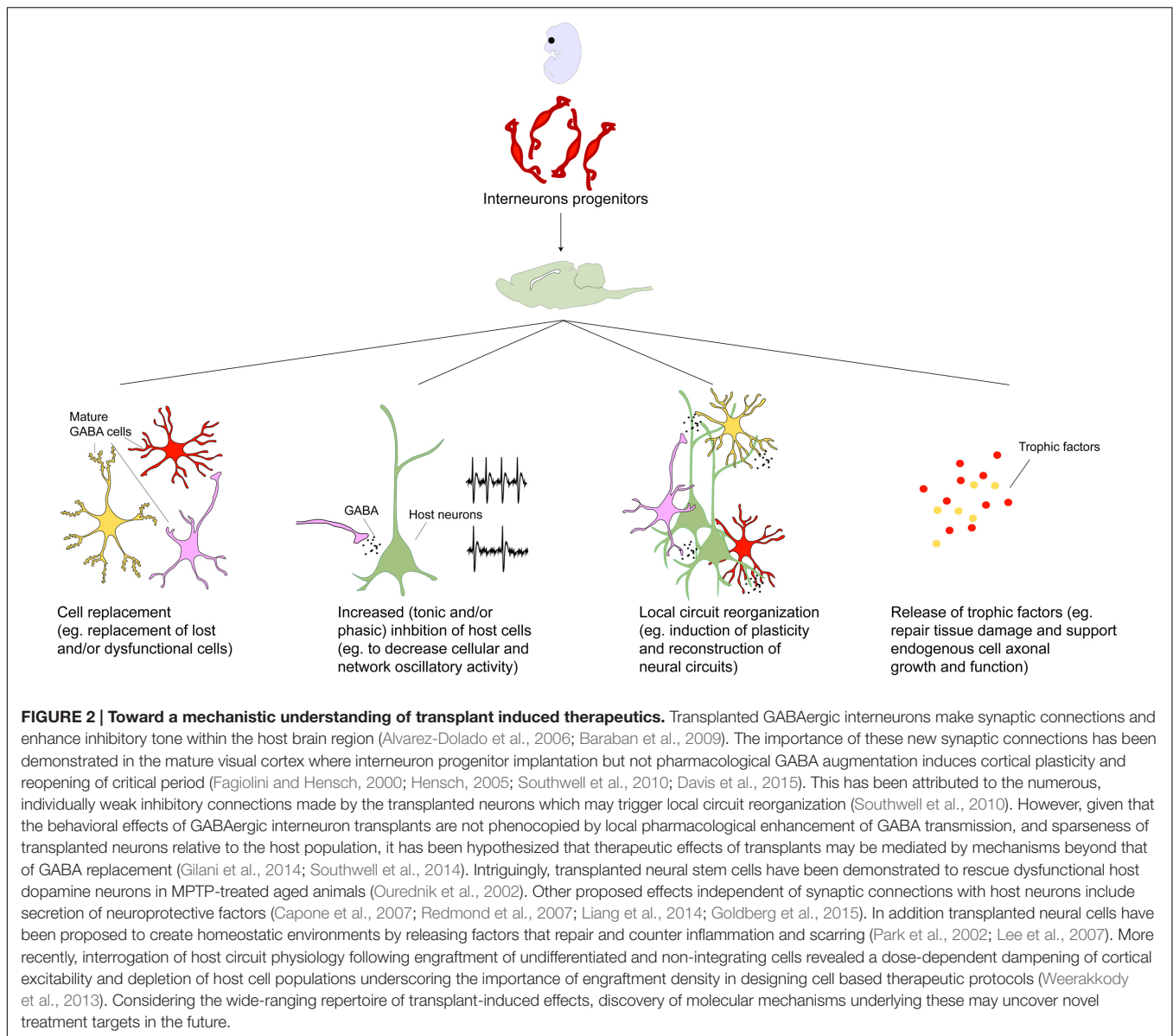


et al., 2009) and granule cells (Henderson et al., 2014), it did not significantly alter IPSC properties of host interneurons (Baraban et al., 2009), whose inhibition is mediated by interneuron subclasses generated from the caudally located CGE cells (Gulyás et al., 1996; Wonders and Anderson, 2006; Caputi et al., 2009). Remarkably, therapeutic efficacy was demonstrated as early as 2.5 weeks following transplantation suggesting possible roles for non-synaptic mechanisms in disease amelioration (Figure 2; De la Cruz et al., 2011). Translational significance of these findings has been tested using transplantation of human pluripotent stem cell derived MGE cells in a pilocarpine-induced temporal lobe epilepsy mouse model (Cunningham et al., 2014; Hunt and Baraban, 2015). While MGE transplants have been shown to increase both synaptic and extrasynaptic inhibition onto host pyramidal neurons (Baraban et al., 2009), activation of extrasynaptic GABA receptors was reported as the basis of MGE precursor transplantation induced amelioration of seizure activity in the cortex (Jaiswal et al., 2015). Given the differential involvement of heterogeneous interneuron populations in the

compensatory and epileptogenic mechanisms, including disease initiation and exacerbation (Cohen et al., 2002; Panuccio et al., 2009), GABA interneuron transplants may prove therapeutic for some types or stages of epilepsy. Key to the success of transplants will be to identify which types or stages of epilepsy can benefit and determine the effective composition of the transplant. This will be aided by rapidly developing technologies that allow high throughput generation of developmentally and functionally distinct interneuron subclasses (Doudna and Charpentier, 2014; Colasante et al., 2015).

SCHIZOPHRENIA AND CORTICAL PLASTICITY

Reductions in SST and PV expressing neurons or functional markers thereof have been observed in the hippocampus and prefrontal cortex in postmortem brains of patients with SCZ (Hashimoto et al., 2003, 2008; Morris et al., 2008; Konradi et al.,



2011). Indeed, disturbances in synchronous cortical oscillations, generated by fast spiking PV neurons (Sohal et al., 2009) and that are correlated with cognitive functions, are a physiological feature of SCZ (Murray et al., 2011). Moreover, increased hippocampal blood volume, a proxy for metabolic activity, a reliable feature of SCZ and correlate of psychosis, can be produced by functional deficits in GABAergic interneurons (Schobel et al., 2013; Gilani et al., 2014).

Exploring the role of cortical interneurons in schizophreniform cognitive deficits in mice, Tanaka et al. (2011) demonstrated that transplantation of MGE cells in the cortex can prevent phencyclidine induced behavioral deficits, possibly via modulation of local cortical circuitry (Southwell et al., 2010; Howard et al., 2014). Moreover, in a genetic mouse model displaying a relatively selective deficit in hippocampal PV interneurons (Glickstein et al., 2007),

transplantation of MGE cells into the hippocampus reversed increased hippocampal activity (as measured with functional magnetic resonance imaging), increased midbrain dopamine neuron activity, increased response to psychostimulants and impaired hippocampus dependent cognition (Gilani et al., 2014). Given the central role of GABA in controlling the timing of critical period plasticity (Hensch, 2005) MGE cells were transplanted in the visual cortex to test whether transplantation of inhibitory cells could induce a plasticity response (Tang et al., 2014). Remarkably, MGE cell transplantation either before (Southwell et al., 2010) or after (Davis et al., 2015) the endogenous critical period induced ocular dominance plasticity and reactivated a new critical period that reversed visual impairments in amblyopic mice. Importantly both PV and SST neuronal populations were shown to be sufficient to drive ocular dominance plasticity but grafts depleted of both PV

and SST populations were not (Tang et al., 2014). Intriguingly, maturing GABA neurons formed numerous but individually weak synaptic connections with host neurons suggesting a potential reorganization of local cortical circuitry. Sufficiency of both PV and SST interneuron populations to induce plasticity in the visual cortex raises an interesting question as to whether the same also holds true for other brain regions and the spinal cord, as it may have implications for developing refined cell based therapies.

ALZHEIMER'S DISEASE

GABAergic control of synaptic plasticity is a key aspect of hippocampus dependent learning as it relates to encoding and retrieval of memories (Paulsen and Moser, 1998). AD patients have been shown to have decreased GABA and SST immunoreactivity in the cerebral cortex (Davies et al., 1980; Grouselle et al., 1998), and in late-onset familial and sporadic AD, the risk gene apolipoprotein (apo) E4 polymorphism exacerbates SST dysfunction (Grouselle et al., 1998). In addition, misfolded proteins such as amyloid- β that are seen in early-onset autosomal dominant AD cause inhibitory interneuron impairments resulting in excitation-inhibition imbalances and network hyperexcitability that is in turn associated with learning and memory deficits (Palop et al., 2007; Andrews-Zwilling et al., 2010; Verret et al., 2012). In particular, PV cell dysfunction has been causally linked to disturbances in cortical network oscillations and cognitive impairments in mice expressing human amyloid precursor protein (Verret et al., 2012). Indeed, AD patients are known to have increased incidence of epileptic events (Amatniek et al., 2006).

In septo-hippocampal lesioned mice, intrahippocampal transplantation of subventricular zone-expanded neural stem cells (Hattiangady and Shetty, 2012) or human embryonic stem cell induced MGE cells (Liu et al., 2013) were shown to reverse learning and memory deficits. Importantly, control experiments involving transplants of spinal progenitors failed to correct these deficits, highlighting the requirement of specific neuronal progenitors in a given target region to achieve functional replacement (Liu et al., 2013). These findings were later extended in two genetic mouse models of AD: apoE4 knock-in mice with or without amyloid- β protein accumulation. Importantly, MGE derived cells showed functional integration in the presence of amyloid aggregation and restored cognitive function thus demonstrating interneuron progenitors' ability to integrate and modify diseased circuits in toxic environments (Tong et al., 2014). Given the strong evidence of impaired synaptic inhibition (Busche et al., 2008) and network oscillatory activity (Amatniek et al., 2006) in AD, GABA cell replacement strategies especially those employing fast spiking PV neurons could be a promising therapeutic avenue.

PARKINSON'S DISEASE

Grafts of dopaminergic cell suspensions into 6-hydroxydopamine (6-OHDA) lesioned striatum are known to restore motor deficits

(Gage et al., 1983). However, a critical limitation of dopaminergic cell grafts is the inability of transplanted cells to disperse in host tissue, limiting the functional recovery to graft site. Intriguingly, local striatal GABAergic interneuron population activity has been shown to sculpt basal ganglia output (Tepper and Bolam, 2004) and abnormalities in inhibitory neurons underlie striatal output imbalances in the dopamine depleted striatum (Mallet et al., 2006). Striatal interneurons may also regulate basal ganglia plasticity (Cazorla et al., 2014) by modulating striatal extrinsic and intrinsic signals and thus may serve as a potential non-dopamine locus to lower striatal activity characteristic of PD.

Neurons derived from transplants of MGE tissue in striatum of the 6-OHDA lesioned mice migrate, functionally integrate and improve motor deficits (Martínez-Cerdeño et al., 2010). Under dopamine depleted conditions, striatopallidal neuronal activity is increased while the opposite is true for striatonigral neurons (Shen et al., 2008). Moreover, selective increase in feed-forward inhibition from local PV interneurons onto striatopallidal neurons enhances neural synchrony (Gittis et al., 2011) which may lead to aberrant β -oscillatory activity characteristic of PD. Overall, GABA tone is increased in the basal ganglia (Borgkvist et al., 2015) leading to persistent suppression of action. Since the transplanted cells show synaptic integration, one possible mechanism of action underlying therapeutic efficacy of MGE cells is the restoration of the balance between the direct and indirect pathways. However, it is notable that a large proportion of donor cells differentiate into oligodendrocytes, implicating non-neuronal support functions provided by the grafts (Figure 2). Intriguingly, MGE transplants made in the subthalamus fail to migrate from the injection site and instead differentiate into glial cells that show long term survival, highlighting the critical role donor-host environmental interactions may play in governing fate of transplanted progenitor cells.

NEUROPATHIC PAIN

In contrast to cortex, inhibitory interneurons form about 30–40% of the total neuronal population in the dorsal horn of the spinal cord. By regulating activity of primary afferents, excitatory interneurons, spinal projection neurons and descending fiber tracts, inhibitory interneurons play a crucial role in maintaining a physiological level of pain sensitivity. Disinhibition within the spinal dorsal horn has long been attributed to the symptoms of NP, e.g., GABA neurotransmission is significantly reduced following nerve injury (Moore et al., 2002; Drew et al., 2004) and GABA agonists can ameliorate allodynia and hyperalgesia (Munro et al., 2009). Impaired inhibition, however, results in multiple cellular, molecular and synaptic changes and therapeutic efficacy of currently available anticonvulsant- and antidepressant-based pharmacological agents is at best symptomatic and constrained by the drugs' broad mechanisms of actions. Given the ability of interneuron progenitors to functionally integrate in neural tissue and modify inhibitory signaling, interneuron transplantation could serve as a potential disease modifying strategy in NP that is without the adverse side effects associated with systemic medications.

Surprisingly, transplanted MGE cells into adult spinal cord differentiate into GABA interneuron populations that integrate with the host spinal cord circuitry (Bráz et al., 2012). Contrary to subthalamic MGE grafts that differentiate into glial cells (Martínez-Cerdeño et al., 2010), MGE derived cells in the spinal cord retain their cortical neurochemical profiles suggesting that the latter does not affect MGE differentiation. More importantly, MGE transplantation reversed mechanical hypersensitivity in a mouse model of peripheral nerve injury (Bráz et al., 2012) and mechanical and heat hyperalgesia in a chemotherapy-induced model of NP (Bráz et al., 2015). Notably, transplantation of cells lacking vesicular GABA transporter failed to rescue paclitaxel-induced pain behavior highlighting the critical role of GABA-mediated modulation of spinal circuits in transplant efficacy in this pain model (Bráz et al., 2015). Given the problems with tolerance and the sedative and addictive properties of traditional pharmacotherapies, interneuron based therapy may be a promising alternative disease modifying therapeutic option.

CHALLENGES AND PITFALLS IN USING MGE PROGENITOR CELL BASED THERAPY

While pre-clinical studies have demonstrated promise for interneuron based therapy, cell based approaches have inherent limitations, including but not limited to unpredictable proliferation, differentiation, and migration, leading to pathological ectopia, including tumors. Addressing these limitations will require greater understanding of the mechanisms governing the development and function of the transplants in different brain regions and at different points in the lifespan of the host (Figure 2). Combined with these challenges, incomplete knowledge of the pathophysiology of vast majority of CNS diseases hinders progress to clinical translation. While excitement surrounds generation of GABAergic interneurons from human pluripotent stem cells (Maroof et al., 2013; Wall et al., 2013), current techniques have yet to achieve sufficient efficiency and specificity. Technological innovations are leading to introduction

of genetic material into transplanted cells to increase specificity, improvement in production methods allowing more rapid amplification, differentiation of stem cells, and use of cell sorting techniques to select cells on the basis of what will comprise a safe transplant designed specifically to improve function in a given brain region. Identifying host characteristics that can aid survival and guide maturation of the grafted cells *in vivo* will also address these challenges.

CONCLUSION

The remarkable capacities of interneuron progenitors to migrate long distances, differentiate into mature interneurons and modify diseased circuits following transplantation have made interneuron based transplantation a viable potential therapeutic approach for CNS diseases. However, further studies in the primate, a refined knowledge of interneuron ontogenesis and development of methods for reliable, high-throughput production of specific GABAergic cell types and safe cell composition of transplants need to be pursued before this approach is realized in the clinical setting. There is reason to be optimistic, given rich and growing literature on interneuron development and rapid growth of technologies that will allow the production of safe and specific transplants.

AUTHOR CONTRIBUTIONS

MC and HM developed concepts. MC wrote and HM edited the paper.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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